Nitrate/Nitrite

Guideline

The maximum acceptable concentration (MAC) for nitrate in drinking water is 45 mg/L. (In cases where nitrite is measured separately from nitrate, the concentration of nitrite should not exceed 3.2 mg/L.)

Identity, Use and Sources in the Environment

Nitrate (NO_3^-) and nitrite (NO_2^-) are naturally occurring ions that are ubiquitous in the environment. Both are products of the oxidation of nitrogen (which comprises roughly 78% of the atmosphere) by micro-organisms in plants, soil or water and, to a lesser extent, by electrical discharges such as lightning.[1] Nitrate is the more stable form of oxidized nitrogen but can be reduced by microbial action to nitrite, which is moderately reactive chemically.

Nitrates are used widely as inorganic fertilizers; almost 400 million kilograms are sold annually in Canada.[2] Nitrates are also used in explosives, as oxidizing agents in the chemical industry and as food preservatives. Nitrites are used mainly as food preservatives, especially in cured meats.

Because of the relative stability of the nitrate ion, most nitrogenous materials in environmental media tend to be converted to nitrates. Therefore, all sources of nitrogen (including organic nitrogen, ammonia and fertilizers) should be considered as potential sources of nitrates. Sources of nitrates in water (particularly groundwater) include decaying plant or animal material, agricultural fertilizers, manure, domestic sewage or geological formations containing soluble nitrogen compounds.[3,4] Nitrites may be produced from excess ammonia in drinking water distribution systems that use chloramines, formed *in situ* from chlorine and ammonia, as a disinfectant.[5]

Because nitrate salts are very soluble, nitrate is highly mobile in soil and migrates readily to the water table when present in excess of the amount utilized by plants as an essential nutrient. Under anaerobic conditions, nitrate may be degraded to nitrite or denitrified.[3] Biological activity in the soil is very important in determining the ultimate fate of nitrate.

Exposure

Water

Nitrate levels in Canadian municipal water supplies are generally less than 5 mg/L.* For example, only six of 59 (10.2%) municipal water supplies sampled in New Brunswick in the summer of 1983 had nitrate levels greater than 4.4 mg/L, and only one of 59 (1.7%) had a nitrate concentration greater than 44 mg/L. In this survey, nitrite levels in the water supplies of most municipalities were below 0.03 mg/L, the highest level reported being 0.3 mg/L.[6] In a 1982 survey of water supplies in Nova Scotia, nitrate levels in 70% of samples of raw and treated water in municipal supplies at 143 sites in 69 communities were less than 0.05 mg/L. The maximum value recorded at one site was 2 mg/L.[7]

Nitrate levels in well water are often higher than those in surface water supplies. In a 1984 survey in an agricultural area of New Brunswick, nitrate concentrations in approximately 20% of the 300 wells sampled exceeded 44 mg/L; some seasonal variation in levels was apparent. Nitrite levels exceeded 3.3 mg/L in only one well at one particular point in time (when the well was contaminated by manure and surface water runoff in April).[8] In an Environment Canada survey of ground-water in the Fraser Valley of British Columbia, 60% of wells (450 samples in 125 locations) were found to have nitrate levels exceeding 45 mg/L. The maximum recorded concentration was 182 mg/L. Mean concentrations of nitrate in B.C. groundwater appear to have gradually increased between 1975 and 1990 because of increased population and intensive agricultural use.[9]

---

* Concentrations of nitrate and nitrite in water are often expressed in the literature in units of nitrate-nitrogen and nitrite-nitrogen, respectively, as follows: 1 mg nitrate-nitrogen/L = 4.43 mg nitrate/L, and 1 mg nitrite-nitrogen/L = 3.29 mg nitrite/L.

Nitrate contamination of groundwaters has also been reported in Ontario (at levels up to 467 mg/L)[4] and Manitoba (at concentrations up to 1063 mg/L).[10]

Food

Vegetables such as beets, celery, lettuce, radishes and spinach contribute about 85 to 90% of an adult's dietary intake of nitrate, with nitrate levels ranging from 1700 to 2400 mg/kg food.[11] Small amounts of nitrates may also be present in fish and dairy products such as cheese. Baked goods and cereals, beets, corn, spinach and turnip greens are major sources of nitrite (2.0 to 4.0 mg/kg food). In Canada, the concentration of nitrates and nitrites in cured meat products has been decreasing as a result of the regulation of such food additives;[12] in the United States, the intake of nitrate/nitrite from cured meats has been estimated to be approximately 10% of dietary intake.[13]

Average daily intakes from food in Canada have been estimated to be 44.3 mg for nitrate and 0.50 mg for nitrite based on a survey of dietary habits.[14] These are consistent with, and in the lower end of the range of, dietary intakes estimated by the World Health Organization (43 to 131 mg/d)[15] and the U.S. Environmental Protection Agency (40 to 100 mg/d).[13]

Air

The annual average concentration of nitrates in ambient air was 0.88 $\mu g/m^3$ in 1990 for 34 communities in 50 sampling locations across Canada.[16] Based on this, the average daily intake of nitrates resulting from inhalation can be estimated to be 18 μg for an adult (daily respiratory volume 20 m^3) and 1.8 μg for an infant (daily respiratory volume 2 m^3). In the United States, intake via air was estimated to range from 25 to 70 $\mu g/d$ for an adult.[13]

Relative Contributions to Intake

The total daily intake of nitrates by adults is estimated to be 51 mg (44.3 mg from food[14] and 6.8 mg from drinking water containing nitrate at a concentration of 4.5 mg/L), or 0.7 mg/kg bw for a 70-kg adult. Ambient air provides a negligible contribution to this total daily intake.

For adults, food is generally the main source of ingested nitrate and nitrite unless drinking water concentrations are above average. In the above calculation of total daily intake using an average concentration in drinking water, food contributes 87% and drinking water 13% to total daily intake. Consumption of 1.5 L of drinking water containing nitrate at concentrations greater than 30 mg/L would contribute more than 50% of a total daily intake of 99 mg (44.3 mg from food and 45 mg from drinking water).

For bottle-fed infants, water used in the preparation of infant formula is generally the main source of nitrates. Consumption of 0.6 L of drinking water containing 4.5 mg/L could contribute 2.7 mg/d or about 0.7 mg/kg bw for a 3- to 5-kg infant. Consumption of water containing 45 mg/L could contribute 27 mg/d or about 7 mg/kg bw. Vegetables such as spinach introduced into the diet at an early age may also contribute to the nitrate/nitrite intake for this population.

Analytical Methods and Treatment Technology

Nitrate and nitrite may be determined in water samples by ion chromatography, in which the ions are separated by ion exchange, converted to their highly conductive acid forms and measured by conductivity.[5,17] The detection limit is 0.1 mg/L as nitrogen.[17] Reduction of nitrate to nitrite by cadmium or hydrazine may also be used for determination of nitrate and nitrite at concentrations up to 45 mg/L, with detection limits of 0.04 mg/L for both methods.[17] A nitrate-selective electrode method is also suitable for nitrate and has a wide range of applicability, from 0.5 to several thousand milligrams per litre.[17] The method of choice would depend on the concentration range expected and on possible interferences from other ions present.

Treatment technologies for removing nitrates and nitrites from drinking water include ion exchange and reverse osmosis.[5,18,19] In one full-scale ion exchange plant, the nitrate concentration was reduced from 16 to 2.6 mg/L.[20] Other treatment methods such as biological denitrification and electrodialysis have also been suggested. Nitrite is normally rapidly oxidized to nitrate in the presence of oxygenated water, and the removal of nitrite may be facilitated by the addition of oxidation agents, if required.[5]

Health Effects

Metabolism

Ingested nitrate is readily absorbed in the upper small intestine and is distributed rapidly throughout the body. Roughly 25% is recirculated into the saliva, where approximately 20% is reduced to nitrite by the oral microflora.[12] If the pH of the stomach is elevated (e.g., in bottle-fed infants, who have low gastric acidity), the growth of nitrate-reducing bacteria is allowed and nitrates are converted to nitrites.[21] Nitrite production increases with age[22] and is enhanced during bacterial infections causing diarrhoea.[21]

Nitrites are rapidly absorbed both in the stomach and in the small intestine. Nitrites may react in the stomach with secondary or tertiary amines and amides present in foods such as cheese or meat to form N-nitroso compounds.[23]

Endogenous synthesis of nitrates, estimated to be about 62 mg/d, occurs in the stomach.[5] This synthesis is greatly increased during gastrointestinal infections, and large amounts of nitrites may also be synthesized depending upon the type of infection.

The human mammary gland does not appear to concentrate nitrate.[24] Transplacental transport of nitrites has been demonstrated in rats in laboratory studies.[25]

Under normal conditions, 80 to 100% of nitrate ingested by infants is excreted in the urine. Urinary excretion of nitrate by adults ranges from 60 to 65% of the amount ingested, with the remainder excreted as ammonia or urea.[15,26] Nitrite is not normally found in urine.

Methaemoglobinaemia

The toxicity of nitrate is thought to be due to its reduction to nitrite. Methaemoglobinaemia, the most commonly reported toxic effect of the ingestion of nitrate-contaminated drinking water, is a condition resulting from the oxidation (by nitrite) of reduced iron, Fe^{2+}, in haemoglobin, the oxygen carrier of mammalian blood, to its oxidized form, Fe^{3+}. The resulting methae-moglobin (MeHb) is unable to release oxygen to body tissues because of its high dissociation constant.[3]

Normal MeHb levels in human blood range from 1 to 3%. Reduced oxygen transport is noted clinically when MeHb concentrations reach 10% or more. Symptoms are cyanosis and, at MeHb concentrations of 80% or more, asphyxia and death. Infants less than three months of age are more susceptible to methaemoglo-binaemia than older infants, children or most adults, with the exception of pregnant women and persons with genetically controlled deficiencies of the enzymes glucose-6-phosphate dehydrogenase or methaemoglobin reductase. Reasons for the greater susceptibility of young infants include their readily oxidizable foetal haemoglobin, their depressed methaemoglobin reductase activity and their incompletely developed capacity to secrete gastric acid and increased susceptibility to gastroenteritis, both of which permit nitrate-reducing bacteria in the gastrointestinal tract to convert nitrate to nitrite.[27]

Between 1945 and 1970, some 2000 cases of methaemoglobinaemia were reported in the world literature.[25] In three early surveys (the United States in 1951, 14 countries in 1962 and Germany in 1964), cases usually involved infants under three months of age and were generally associated with nitrate levels in drinking water greater than 100 mg/L.[15] Epidemiological evidence gathered in the 1951 study indicated that no cases of methaemoglobinaemia had been reported in the United States when water containing nitrate at concentrations below 45 mg/L had been consumed.[28] Very few cases (3.0% and 4.4%, respectively) of

methaemoglobinaemia were reported at nitrate concentrations below 50 mg/L in the 1962 and 1964 surveys. However, the nitrate concentrations were unknown in 32%, 56% and 67% of the cases in the three surveys, respectively, and bacterial infections, which greatly increase endogenous nitrate and nitrite synthesis, were not considered as confounding factors.[15]

In Hungary in 1975 to 1977, 190 cases of methaemoglobinaemia were reported, 94% in infants less than three months of age. The nitrate level in drinking water was more than 100 mg/L in 92% of cases and between 40 and 100 mg/L in the remaining 8%.[15] In 1982, 96 cases of methaemoglobinaemia were reported. All cases were associated with privately dug wells, and 92% of the patients were three months of age or younger. Nitrate levels in drinking water were above 100 mg/L in 93% of cases and between 40 and 100 mg/L in the remaining 7%.[15]

The prevalence of subclinical methaemoglo-binaemia (<10% MeHb) in infants as related to ingestion of nitrate in drinking water has also been examined. In a study of 256 Californian infants less than six months of age, there was no association between the frequency of elevated MeHb levels and nitrate intake, calculated from the history of ingestion and measured levels in well water (which occasionally exceeded 44 mg/L) and formula.[29] The highest MeHb levels (>6% MeHb) were found in babies with respiratory illness or diarrhoea. In Israel, there were no differences between the mean MeHb levels in 1702 infants from communities with well water containing 50 to 90 mg nitrate/L and in 758 infants from control areas (5 mg/L in the water supply).[25] However, only 6% of the infants studied received formula made up with tap water; the remainder were breast-fed and/or received cows' milk. In contrast, in a study of 486 Southwest African/ Namibian infants, there was a strong association between nitrate concentrations in drinking water and MeHb levels. In the "high exposure" region (>20 mg nitrate/L), 33% of infants had more than 3% MeHb; in the "low exposure" region (<20 mg nitrate/L), MeHb levels in only 13% of the infants exceeded this value.[30]

Older children appear to be less susceptible than young infants to methaemoglobinaemia. For example, in a recent U.S. study of 102 children one to eight years of age, there was no association between MeHb levels and ingestion of water with nitrate concentrations ranging from 44 to 500 mg/L.[27] In contrast, an average MeHb level of 5.3% was reported for 11 Russian school-children aged 12 to 14 ingesting drinking water containing a mean nitrate level of 105 mg/L. This was a statistically significant increase (p <0.001) over the mean level (0.75% MeHb) in 10 children drinking water with lower concentrations (mean 8 mg/L). The authors

also reported slowing of conditioned motor reflexes in response to visual and auditory stimuli in the high exposure group.[31]

It is difficult to interpret quantitative data on the association between nitrate/nitrite intake and infantile methaemoglobinaemia, for several reasons. Reported data on nitrate levels in drinking water associated with methaemoglobinaemia are often inaccurate, particularly when samples for analysis are obtained weeks or months after the acute illness, during which time the nitrate concentration may have changed considerably. In addition, the sources of the drinking water consumed by the affected infants in most studies were shallow wells that were almost certainly contaminated with bacteria; this confounding factor complicates interpretation of the data, because infections may increase endogenous nitrate and nitrite synthesis. As well, most studies did not take into account any additional intakes of nitrate or nitrite from other sources. Finally, the nitrate level in water is only one factor in the etiology of methaemoglo-binaemia (e.g., intake of vitamin C may be important[15]), and there are also large variations in individual susceptibility.

Carcinogenicity

In the human stomach, nitrites can react with nitrosatable compounds, such as amides and amines, to form N-nitroso compounds. Some N-nitroso compounds are potent carcinogens in animal species[23,32] and are therefore probably carcinogenic in humans.[33]

Epidemiological evidence linking intake of nitrite and nitrate with gastric cancer in humans has been equivocal, with some studies indicating a positive correlation[34,35] and others showing no such association.[36,37]

Some evidence for an association between the ingestion of nitrate and the incidence of stomach cancer has been obtained in descriptive epidemiological studies conducted in Chile (133 to 499 ppm in vegetables);[36,38] Colombia (<40 mg/L in well water);[39] England (90 mg/L,[40] 25 mg/L[41] and 50 mg/L[42] in drinking water); Italy (<20 mg/L in drinking water);[43] Denmark (<30 mg/L in drinking water);[44] Hungary (<100 mg/L in drinking water);[45] and Singapore (215 mg/d in food).[35] In contrast, no evidence of an association between ingestion of nitrate and stomach cancer was obtained in descriptive epidemiological studies conducted in France (93% under 43 mg/L in drinking water)[46] and the United Kingdom (<50 mg/L in drinking water;[47] and total nitrate intake 69.4 to 124.9 mg/d, total nitrite intake 4.67 to 7.06 mg/d[37]).

Individual exposure to nitrate has not been estimated in any of the descriptive epidemiological studies conducted to date, nor have confounding factors such as intake of vitamin C (a well-known inhibitor of the nitrosation reaction[21]), gastric acidity, concurrent bacterial infection and the decline in mortality rates due to gastric cancer in recent decades[22,47] been adequately taken into account. Closer examination of some of the above descriptive studies reveals inconsistencies that reduce the significance of the positive associations; for example, biological monitoring in several studies revealed high nitrate levels in people from both low-risk and high-risk groups.[15,36,39,44]

Few case–control (analytical) studies on cancer and nitrates or nitrites have been carried out. In a Canadian case–control study on diet and stomach cancer,[34] 246 cases from Manitoba, Newfoundland and Metropolitan Toronto were matched to 246 randomly selected controls from the same areas. Daily consumption of nitrates, nitrites, vitamins, fresh vegetables, preserved meat, etc. was estimated from a detailed diet history questionnaire. Nitrates from food were associated with a decreased risk of gastric cancer (odds ratio [OR] = 0.66, p = 0.00002), whereas nitrites from food were associated with an increased risk (OR = 1.7, p = 0.0006). Other factors that reduced risk included vitamin C and citrus fruit; this could possibly explain the reduction in risk from nitrates, most of which came from green leafy vegetables high in vitamin C. Nitrate intake from drinking water was not examined, other than the observation of a slight decrease in risk for those on public water supplies compared with those on private wells (OR = 0.86, p = 0.03).

In a case–control study of gastric cancer precursor lesions conducted in a high-risk black population in southern Louisiana, higher gastric juice nitrate concen-trations were associated with more severe lesions in one population, whereas the reverse trend was observed in a second population.[48] The authors suggested that this phenomenon was attributable to the different sources of nitrates in the two populations: in the first population, nitrate came mostly from drinking water, whereas in the second population, nitrate came mostly from fresh fruits and fresh green, leafy vegetables, which apparently exerted a protective effect.

There has been no evidence from chronic animal studies conducted to date that nitrate is carcinogenic.[12,49] The results from animal studies on the carcinogenicity of nitrites have been contradictory. In a review of a number of animal carcinogenicity studies to 1980 (most of which were judged inadequate), the U.S. National Academy of Sciences judged that there was insufficient evidence to conclude that either nitrate or nitrite was carcinogenic.[12]

Several studies in rats fed sodium nitrite in the diet or via drinking water have found an increased incidence of tumours,[50,51] whereas others have failed to show a positive link between nitrite intake and tumour incidence.[49,52] For example, a small but statistically

significant increase in squamous papillomas of the forestomach was observed in eight of 45 (18%) MRC Wistar rats receiving 3000 mg sodium nitrite/L in drinking water for at least one year and maintained for life; only two of 91 (2%) controls developed these tumours.[50] Benign liver tumours were also induced in male Wistar rats receiving 800 and 1600 mg sodium nitrite/kg food (approximately 40 and 80 mg/kg bw) for 92 weeks; at the end of the dosing period, the incidence of tumours in the high-dose group (5/19) was statistically significantly elevated (p <0.05) over that (0/19) in the controls. It should be noted that only a few animals of one sex were tested in this study.[51]

In contrast, in two studies in which sodium nitrite was administered to F344 rats in drinking water for two years at levels of 1250 or 2500 mg/L and sodium nitrate was given in the diet at levels of 2.5 or 5%, a significant protective effect was observed; there was a significant decrease in tumour incidence in the high-dose females given nitrite compared with controls, and a reduction in the incidence of mononuclear cell leukaemias in the experimental groups was observed in both studies. Although a variety of tumours occurred in all groups, including controls, they were not considered to be dose-related.[49] In a study in which sodium nitrite was fed to male F344 rats in the diet at dose levels of 0.2 or 0.5% for up to 115 weeks, the incidence and time of onset of tumours (lymphomas, leukaemias and testicular interstitial cell tumours) were reduced in a dose-related manner, which correlated with a similar trend in body weights.[52]

Mutagenicity

Nitrate is not mutagenic in bacteria and mammalian cells *in vitro*.[26] Nitrate contamination of drinking water was found not to be associated with peripheral lymphocyte sister chromatid exchange frequencies in humans.[53] Chromosomal aberrations were observed in the bone marrow of rats after oral nitrate uptake, but this could have been due to exogenous N-nitroso compound formation.[26]

There is some evidence that nitrites or nitrosation reaction products are mutagenic. Sodium nitrite induced cytogenetic damage *in vivo* in rats, mice and rabbits and *in vitro* in BSC-1 and HeLa cells.[54] Addition of nitrite to normal human fasting gastric juice at levels close to 30 times those obtained after a nitrite-rich meal caused mutation in *Salmonella typhimurium* strain TA1537.[55] There is also evidence from experiments with embryonic cells of Syrian golden hamsters that nitrites are transplacental mutagens.[56]

Reproductive Effects and Teratogenicity

The results of a recent Australian study of 218 case–control pairs suggested that there may be an association between the estimated nitrate concentration of water consumed during pregnancy and congenital malformations. A nearly threefold increase in risk of bearing a malformed child was reported for women who drank water containing 5 to 15 mg nitrate/L; the increase was fourfold for levels greater than 15 mg/L.[57] The accuracy of the estimated nitrate levels in this study has, however, been questioned.[58] In addition, the elevation in risk for all malformations observed in this study seemingly weakens the hypothesis that nitrates are causally associated with these anomalies. Moreover, the findings have not been confirmed by the preliminary results of an ecological epidemiological study in eastern England[59] and a case–control study in New Brunswick.[60] In the latter, nitrate concentrations in the water supply were not statistically associated with central nervous system birth defects. Although the direction of the causal association (risk odds ratio = 1.04, 1.22 and 2.30 for exposure to levels of 1.25, 6.25 and 26 mg/L, respectively) was the same as that reported in the Australian study, the strength of the association was not as great.

Nitrite has not been found to be teratogenic in rats administered 80 mg/kg bw on day 15 of pregnancy[61] or in mice administered 80 or 110 mg/kg bw during pregnancy.[62] However, overall progeny yield was significantly reduced, and there were small decremental effects on litter size, perinatal survival and weanling weight following administration of 1 g sodium nitrite/L in drinking water to mice before and during pregnancy.[63] Transient increases in MeHb level and impaired motor function have also been observed in weanling mice of mothers exposed to 110 mg sodium nitrite/kg bw during pregnancy.[62]

Other Effects

The results of preliminary studies indicate that there may be some behavioural effects associated with the ingestion of nitrate in drinking water; this aspect warrants further study. The results of a limited study of a small number of subjects in the former Soviet Union indicated that the conditioned motor reflexes of 39 children ingesting drinking water containing approximately 105 mg nitrate/L were significantly slower than those of 20 children drinking water with lower concentrations (approximately 8 mg nitrate/L).[31] Small changes in perceptual vigilance have also been observed in 20 female adult subjects administered a high sublingual dose of sodium nitrate (0.1 mL containing 22 500 ppm).[64]

A significant reduction of overall motor activity in mice exposed to 1500 or 2000 mg sodium nitrite/L in drinking water has been reported, and irreversible brain electrical changes have been noted in rats following chronic exposure to 100 mg sodium nitrate/L.[25]

Classification and Assessment

Although an association between the ingestion of nitrate/nitrite in drinking water and gastric cancer has been observed in some of the descriptive and analytical epidemiological studies conducted to date, no firm conclusions concerning causality can be drawn because of the limitations of the available data. There is, however, some concern about an increased risk of cancer in humans because of the fact that nitrites derived from nitrates may react with certain foods *in vivo* to form carcinogenic N-nitroso compounds. Nitrate has not been found to be carcinogenic in chronic animal studies; the results of similar investigations with nitrite have been equivocal. Nitrate/nitrite have, therefore, been included in Group IIIA (possibly carcinogenic to humans), although the weight of evidence is weak.

For compounds classified in Group IIIA, the acceptable daily intake (ADI) is normally derived on the basis of division of a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-effect level (LOAEL) by appropriate uncertainty factors.

The critical effect associated with the ingestion of nitrate/nitrite in drinking water is methaemoglobinaemia, the development of which requires the presence of nitrite. The most sensitive subpopulation is infants less than three months of age.

It is difficult to establish a LOAEL or NOAEL for infantile methaemoglobinaemia because of difficulties in interpretation of data, as discussed earlier. Although reported data on nitrate levels in drinking water associated with methaemoglobinaemia are often inaccurate, it can be concluded that most cases of clinical infantile methaemoglobinaemia associated with the ingestion of nitrate in drinking water have occurred at levels exceeding 100 mg nitrate/L; this level is therefore considered to be the LOAEL. Although levels as low as 40 mg/L were found to be associated with elevated MeHb levels in two Hungarian studies,[15] most, if not all, cases were associated with privately dug wells and quite likely involved bacterial contamination, which would greatly increase the conversion of nitrate to nitrite.

Increases in subclinical MeHb levels (<10%) have been reported in infants ingesting drinking water containing nitrate at concentrations as low as 20 mg/L;[30] however, this study was carried out in a developing country, where bacterial contamination of the drinking water is likely and other dietary conditions are different from those in Canada. As well, such an association has not been observed in other studies of infants consuming drinking water with higher nitrate levels (e.g., 50 to 90 mg/L).[25] The significance, if any, of these subclinical MeHb levels in infancy and childhood remains unclear.[15]

An early U.S. study found that no cases of methaemoglobinaemia had been reported following consumption of water containing less than 45 mg nitrate/L.[28] This is therefore considered as the NOAEL and is consistent with other studies in which the NOAELs are in the range 40 to 50 mg/L.[15]

Rationale

On the basis of the available data, a maximum acceptable concentration (MAC) for nitrate in drinking water of 45 mg/L, expressed as nitrate, is reaffirmed/ recommended. (This is equal to 10 mg/L as nitrate-nitrogen.) This value has been derived based on the NOAEL for infantile methaemoglobinaemia of 45 mg/L observed in a North American population.

The application of an uncertainty factor to this NOAEL is not deemed necessary, for a number of reasons: the NOAEL applies to the most susceptible and sensitive subgroup of the population (bottle-fed infants less than three months of age) and therefore will be protective of the general population; most infants exhibit no signs of toxicity until the LOAEL (approximately twice the NOAEL) is reached; there is evidence that numerous other environmental factors (e.g., vitamin C intake) play an important role in the etiology of nitrate- and nitrite-related diseases; and most studies failed to account for such confounding factors as bacterial contamination of the drinking water, which could have been responsible for much of the observed methaemoglobinaemia at higher levels. These same dietary and environmental factors are important in the conversion of nitrate to nitrite and the possible production of carcinogenic N-nitroso compounds from nitrite.

Although the guideline is based principally on effects in the most sensitive subgroup (i.e., infants), it is considered prudent to minimize exposure of the entire population to nitrate owing to suggestive evidence of an association in several populations between gastric cancer and moderate levels of nitrate in drinking water. The guideline is therefore intended to apply to both children and adults.

Nitrite is directly toxic and is converted endogenously from nitrate at an average rate of 5 to 10%. A relative potency for nitrite and nitrate of 10 to 1 (on a molar basis) with respect to methaemoglobinaemia formation has been suggested,[65] and an uncertainty factor of 10 should be applied to the NOAEL for nitrate to derive a guideline for nitrite. A maximum of 3.2 mg nitrite/L is therefore recommended in cases where nitrite and nitrate are determined separately.

References

1.   Beatson, C.G. Methaemoglobinaemia—Nitrates in drinking water. Environ. Health, 86: 31 (1978).

2.   Agriculture Canada. Canadian fertilizer consumption, shipments and trade, 1990/1991. Policy Branch, Ottawa (1991).

3.   Adam, J.W.H. Health aspects of nitrate in drinking-water and possible means of denitrification (literature review). Water SA, 6: 79 (1980).

4.   Egboka, B.C.E. Nitrate contamination of shallow groundwaters in Ontario, Canada. Sci. Total Environ., 35: 53 (1984).

5.   World Health Organization. Analytical and water treatment methods for health-based guideline values. Report on a WHO consultation, Medmenham, U.K., 27–29 January. WHO Regional Office for Europe, Copenhagen (1992).

6.   Environment New Brunswick. Chemistry of municipal water supplies in New Brunswick. Internal Report D83-01, Fredericton (1983).

7.   Nova Scotia Department of Health. Chemical quality. Municipal water supplies. Halifax (1982).

8.   Ecobichon, D.J., Allen, M. and Hicks, R. The contamination of groundwater by agrochemicals as determined by a well water quality study in Carleton County: a report, 1984–1985. New Brunswick Department of Health, Fredericton, June (1985).

9.   Liebscher, H., Hii, B. and McNaughton, D. Nitrate and pesticide contamination of ground water in the Abbotsford aquifer, southwestern British Columbia. Inland Waters Directorate, Environment Canada, Vancouver (1992).

10.   Kjartanson, K. Memorandum to Dr. P. Toft, Department of National Health and Welfare, dated 2 June, from K. Kjartanson, Environmental Management, Manitoba Environment and Workplace Safety and Health (1986).

11.   Corre, W.J. and Breimer, T. Nitrate and nitrite in vegetables. Centre for Agricultural Publishing and Documentation, Wageningen (1979).

12.   Committee on Nitrite and Alternative Curing Agents in Food. The health effects of nitrate, nitrite, and N-nitroso compounds. National Research Council, National Academy Press, Washington, DC (1981).

13.   U.S. Environmental Protection Agency. Nitrate and nitrite. Proposed rules. Fed. Regist., 50(219): 48972 (1985).

14.   Choi, B.C.K. N-nitroso compounds and human cancer: a molecular epidemiologic approach. Am. J. Epidemiol., 121(5): 737 (1985).

15.   World Health Organization. Health hazards from nitrates in drinking-water. Report on a WHO meeting. WHO Regional Office for Europe, Copenhagen (1985).

16.   Environment Canada. National Air Pollution Surveillance (NAPS) annual summary 1990. Environmental Protection Service Report EPS 7/AP/23 (1992).

17.   American Water Works Association/American Public Health Association/Water Pollution Control Federation. Standard methods for the examination of water and wastewater. 17th edition. American Public Health Association, Washington, DC (1989).

18.   Department of National Health and Welfare. Guidelines for Canadian drinking water quality. Water treatment principles and applications: a manual for the production of drinking water. Working draft. Ottawa (1992).

19.   U.S. Environmental Protection Agency. National primary drinking water regulations—unregulated contaminants monitoring and synthetic organic chemicals and inorganic chemicals. Fed. Regist., 56(20): 3526 (1991).

20.   Lauch, R.P. and Guter, G.A. Ion exchange for the removal of nitrate from well water. J. Am. Water Works Assoc., 78(5): 256 (1986).

21.   Hartman, P.E. Review: putative mutagens and carcinogens in foods. 1. Nitrate/nitrite ingestion and gastric cancer mortality. Environ. Mutagen., 5: 111 (1983).

22.   Turek, B., Hlavsova, D., Tucek, J., Waldman, J. and Cerna, J. The fate of nitrates and nitrites in the organism. IARC Sci. Publ., 31: 625 (1980).

23.   Broitman, S.A., Velez, H. and Vitale, J.J. A possible role of iron deficiency in gastric cancer in Colombia. Adv. Exp. Med. Biol., 135: 155 (1981).

24.   Green, L.C., Tannenbaum, S.R. and Fox, J.G. Nitrate in human and canine milk. N. Engl. J. Med., 306: 1367 (1982).

25.   Shuval, H.I. and Gruener, N. Epidemiological and toxicological aspects of nitrates and nitrites in the environment. Am. J. Public Health, 62: 1045 (1972).

26.   Speijers, G.J.A., Van Went, G.F., Van Apeldoorn, M.E., Montizaan, G.K., Janus, J.A., Canton, J.H., Van Gestel, C.A.M., Van der Heijden, C.A., Heijna-Merkus, E., Knaap, A.G.A.C., Luttik, R. and De Zwart, D. Integrated criteria document nitrate. Appendix to Report No. 758473012, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands (1989).

27.   Craun, G.F., Greathouse, D.G. and Gunderson, D.H. Methaemoglobin levels in young children consuming high nitrate well water in the United States. Int. J. Epidemiol., 10: 309 (1981).

28.   Walton, R. Survey of literature relating to infant methaemoglobinaemia due to nitrate-contaminated water. Am. J. Public Health, 41: 986 (1951).

29.   Shearer, L.A., Goldsmith, J.R., Young, C., Kearns, O.A. and Tamplin, B.R. Methemoglobin levels in infants in an area with high nitrate water supply. Am. J. Public Health, 62: 1174 (1972).

30.   Super, M., de V. Heese, H., MacKenzie, D., Dempster, W.S., du Plessis, J. and Ferreira, J.J. An epidemiological study of well-water nitrates in a group of South West African/Namibian infants. Water Res., 15: 1265 (1981).

31.   Petukhov, N.I. and Ivanov, A.V. Investigation of certain psychophysiological reactions in children suffering from methemoglobinemia due to nitrates in water. Hyg. Sanit., 35: 29 (1970).

32.   Hathcock, J.N. Nutritional toxicology. Vol. 1. Academic Press, New York, NY (1982).

33.   Fraser, P. Nitrates: epidemiological evidence. IARC Sci. Publ., 65: 183 (1985).

34.   Risch, H.A., Jain, M., Choi, N.W., Fodor, J.G., Pfeiffer, C.J., Howe, G.R., Harrison, L.W., Craib, K.J.P. and Miller, A.B. Dietary factors and the incidence of cancer of the stomach. Am. J. Epidemiol., 122: 947 (1985).

35.   Dutt, M.C., Lim, H.Y. and Chew, R.K.H. Nitrate consumption and the incidence of gastric cancer in Singapore. Food Chem. Toxicol., 25(7): 515 (1987).

36.   Armijo, R., Gonzalez, A., Orellana, M., Coulson, A.H., Sayre, J.W. and Detels, R. Epidemiology of gastric cancer in Chile: 2. Nitrate exposure and stomach cancer frequency. Int. J. Epidemiol., 10: 57 (1981).

37.   Forman, D., Al-Dabbagh, S. and Doll, R. Nitrates, nitrites and gastric cancer in Great Britain. Nature, 313: 620 (1985).

38.   Armijo, R., Orellana, M., Medina, E., Coulson, A.H., Sayre, J.W. and Detels, R. Epidemiology of gastric cancer in Chile: 1. Case–control study. Int. J. Epidemiol., 10: 53 (1981).

39.   Cuello, C., Correa, P., Haenszel, W., Gordillo, G., Brown, C., Archer, M. and Tannenbaum, S. Gastric cancer in Colombia. 1. Cancer risk and suspect environmental agents. J. Natl. Cancer Inst., 57: 1015 (1976).

40.   Hill, M.J., Hawksworth, G.M. and Tattersall, G. Bacteria, nitrosamines and cancer of the stomach. Br. J. Cancer, 28: 562 (1973).

41.   Fraser, P. and Chilvers, C. Health aspects of nitrate in drinking water. Sci. Total Environ., 18: 103 (1981).

42.   Clough, P.W.L. Nitrates and gastric carcinogenesis. Minerals Environ., 5: 91 (1983).

43.   Gilli, G., Corrao, G. and Favilli, S. Concentrations of nitrates in drinking water and incidence of gastric carcinomas: first descriptive study of the Piemonte Region, Italy. Sci. Total Environ., 34: 35 (1984).

44.   Jensen, O.M. Nitrate in drinking water and cancer in Northern Jutland, Denmark, with special reference to stomach cancer. Ecotoxicol. Environ. Saf., 6: 258 (1982).

45.   Juhasz, L., Hill, M.J. and Nagy, G. Possible relationship between nitrate in drinking water and incidence of stomach cancer. IARC Sci. Publ., 31: 619 (1980).

46.   Vincent, P., Dubois, G. and Leclerc, H. Nitrate in drinking water and cancer mortality. Epidemiological study in the north of France. Rev. Epidemiol. Santé Publique, 31: 199 (1983).

47.   Beresford, S.A.A. Is nitrate in the drinking water associated with the risk of cancer in the urban UK? Int. J. Epidemiol., 14: 57 (1985).

48.   Fontham, E., Zavala, D., Correa, P., Rodriguez, E., Hunter, F., Haenszel, W. and Tannenbaum, S.R. Diet and chronic atrophic gastritis: a case–control study. J. Natl. Cancer Inst., 76: 621 (1986).

49.   Maekawa, A., Ogiu, T., Onodera, H., Furuta, K., Matsuoka, C., Ohno, Y. and Odashima, S. Carcinogenicity studies of sodium nitrite and sodium nitrate in F-344 rats. Food Chem. Toxicol., 20: 25 (1982).

50.   Mirvish, S.S., Bulay, O., Runge, R.G. and Patil, K. Study of the carcinogenicity of large doses of dimethylnitramine, N-nitroso-L-proline, and sodium nitrite administered in drinking water to rats. J. Natl. Cancer Inst., 64: 1435 (1980).

51.   Aoyagi, M., Matsukura, N., Uchida, E., Kawachi, T., Sugimura, T., Takayama, S. and Matsui, M. Induction of liver tumors in Wistar rats by sodium nitrite given in pellet diet. J. Natl. Cancer Inst., 65: 411 (1980).

52.   Grant, D. and Butler, W.H. Chronic toxicity of sodium nitrite in the male F344 rat. Food Chem. Toxicol., 27(9): 565 (1989).

53.   Kleinjans, J.C.S., Albering, H.J., Marx, A., van Maanen, J.M.S., van Agen, B., ten Hoor, F., Swaen, G.M.H. and Mertens, P.L.J.M. Nitrate contamination of drinking water: evaluation of genotoxic risk in human populations. Environ. Health Perspect., 94: 189 (1991).

54.   Luca, D., Luca, V., Cotor, F. and Rileanu, L. *In vivo* and *in vitro* cytogenetic damage induced by sodium nitrite. Mutat. Res., 189: 333 (1987).

55.   Gatehouse, D.G. and Tweats, D.J., Mutagen formation after the addition of nitrite to normal human gastric juice. Carcinogenesis, 3: 597 (1982).

56.   Inui, N., Nishi, Y., Taketomi, M. and Mori, M. Transplacental action of sodium nitrite on embryonic cells of Syrian golden hamster. Mutat. Res., 66: 149 (1979).

57.   Dorsch, M.M., Scragg, R.K.R., McMichael, A.J., Baghurst, P.A. and Dyer, K.F. Congenital malformations and maternal drinking water supply in rural South Australia: a case–control study. Am. J. Epidemiol., 119: 473 (1984).

58.   Arbuckle, T.E., Hewitt, D. and Sherman, G.J. Re: "Congenital malformations and maternal drinking water supply in rural South Australia: a case–control study." Am. J. Epidemiol., 124: 344 (1986).

59.   Fraser, P. Personal communication. Epidemiological Monitoring Unit, London School of Hygiene and Tropical Medicine, London, U.K. (1987).

60.   Arbuckle, T.E. Water nitrates and CNS birth defects in New Brunswick 1973–1983. M.Sc. thesis, University of Toronto, Toronto, September (1986).

61.   Khera, K.S. Reduction of teratogenic effects of ethylenethiourea in rats by interaction with sodium nitrite *in vivo*. Food Chem. Toxicol., 20: 273 (1982).

62.   Kinoshita, S. Effects of sodium nitrite administered to the pregnant mice on the motor function of their weanlings. Nippon Koshu Eisei Zasshi, 29: 510 (1982).

63.   Anderson, L.M., Giner-Sorolla, A., Ebeling, D. and Budinger, J.M. Effects of imipramine, nitrite, and dimethylnitrosamine on reproduction in mice. Res. Commun. Chem. Pathol. Pharmacol., 19: 311 (1978).

64.   Rotton, J., Tikofsky, R.S. and Feldman, H.T. Behavioral effects of chemicals in drinking water. J. Appl. Psychol., 67: 230 (1982).

65.   World Health Organization. WHO guidelines for drinking-water quality. Vol. 2. Health criteria and other supporting information. Geneva (in press).